11.2 Statistical Analysis

Primary Biomarker Variable Analysis

The difference in 1,3-butadiene metabolites (in daily excreted amount) and acrolein (3-HPMA) (in daily excreted amount) among the two treatment groups will be examined via linear mixed model for analysis of variance of repeated measurements. The model will include terms for subject, treatment and time. Multiplicity adjustment will be considered. The response variables will be adjusted by number of cigarettes smoked per day. The null hypothesis to be tested is that smokers treated with SCoR2003-6 (test cigarette J 5) will not differ in the two primary biomarkers compared to smokers treated with Marlboro Ultra Lights.

Secondary Biomarker Variable Analysis

The difference in total nicotine equivalent, NNAL and carboxyhemoglobin among the two treatment groups will be analyzed in the secondary biomarker analysis. The same statistical model as used in the primary biomarker analysis will be used for variables with 2 or more repeated measurements and analysis of variance will be used for the remaining variables. Multiplicity adjustment will be considered.

Other Analysis of Biomarker Variables

Biomarker variables including plasma cotinine, and mutagenic substances in urine as measured by the Ames test, blood pressure, pulse rate, body weight, HDL-cholesterol, LDL-cholesterol, HS C-reactive protein, fibrinogen, von Willebrand Factor, albumin, 11-dehydro-thromboxane-B_2, 8-Epi-Prostaglandin F_{2_α}, total anti-oxidant capacity, and hematology (hemoglobin, hematocrit, WBC with differential, RBC, and platelet count) will also be considered. The same statistical models as used in the secondary biomarker analysis will be used. Multiplicity will not be adjusted.

Descriptive statistics will be calculated for all biomarkers by treatment (A and B) and smoking group stratification (10-19 cigarettes/day and 20-30 cigarettes/day) on each assessment day. Corresponding graphs over study week will be presented. Change from baseline (Week 0, Day 8 of SCoR2003-6/01/02) at each assessment week will also be calculated and summarized by descriptive statistics with graphs showing trend across study days. Change for each time point will also be examined with the same statistical model as used for the primary and secondary biomarker variables analysis. Descriptive statistics after adjusting for number of cigarettes smoked per day will also be calculated for each biomarker.

Linear regression will be fitted for each biomarker versus number of cigarette smoked per day and versus total nicotine equivalent. Fitted regression lines will be presented as graphs.

Smoking Topography Analysis

Smoking topography measurements include number of puffs, puff volume, puff duration, inter-puff interval, and peak flow. Descriptive statistics will be used to summarize these variables by treatment, smoking group stratification, and assessment day.

Questionnaire Analysis

The Product Assessment questionnaire will be completed at Weeks 0 (baseline, Day 8 of SCoR2003-6/01/02), 4, 8, 12, 16, 20, and 24. The total number (frequency) of subjects answering each rating will be calculated for each question. Frequencies will be presented for each assessment day by treatment and smoking stratification. Change from baseline as measured by shift in the ratings may be examined to explore trends during the study.

Safety Analysis

Safety variables assessed in the study include adverse events, vital signs, ECG, clinical chemistry, urinalysis, and physical examination. All safety data will be presented for each subject and summarized descriptively. Adverse events will be coded using the MedDRA adverse event dictionary and summarized by preferred term within body system. Any clinically significant findings will be discussed.

11.3 Determination of Sample Size

Based on a previous study, the difference in HPMA (ng/24hr) between SCoR2003-6 (test cigarette J 5) and Marlboro Ultra Lights is likely to be around 0.68 with a common standard deviation not exceeding 0.59. For a two-sided test and 5% Type I error rate, a sample size of 20 subjects for each group will provide at least 80% power to detect such a difference and variability between the two treatment groups.

A sample size of 50 subjects for the SCoR2003-6 (test cigarette J 5) group and 25 for Marlboro Ultra Lights group is also for practical considerations. Knowledge about the variability of the primary biomarkers is limited.